CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PROFENOPHOS

Chemical Code # 002042, Tolerance # 00404
SB 950 # 253

June 16, 1997
Revised: 4/3/98

I. DATA GAP STATUS

Combined (chronic/onco), rat:	No data gap, no adverse effect.
Chronic toxicity, dog:	No data gap, possible adverse effect.
Oncogenicity, mouse:	No data gap, no adverse effects.
Reproduction, rat:	No data gap, no adverse effects.
Teratology, rat:	No data gap, no adverse effects.
Teratology, rabbit:	No data gap, no adverse effects.
Gene mutation:	No data gap, no adverse effects
Chromosome effects:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	No data gap, no adverse effects.

Toxicology one-liners are attached.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.
Studies reviewed through volume #: 404-165, record #: 159648

File name: T980403
Original: Kishiyama & Silva, 6/16/97; Silva, 4/3/98

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

CHRONIC TOXICITY, RAT

024 978898: A.J. Marias, Twelve-Month Status report - "Two-Year Chronic Oral Toxicity Study with Technical CGA 15324 in Albino Rats", IBT No. 622-06895, [8/28/71]. CGA 15324 Technical, purity not stated, was admixed with the feed at concentrations of 0, 0.2, 1, 20, or 200 ppm and fed to 60 albino rats for 2 years. Cholinesterase inhibition reported for 20 and 200 ppm groups. UNACCEPTABLE. Insufficient information for assessment; Non-validated study. (J. Remsen, 7/12/85).

** 009, 086 978894, 115629 "Two-Year Chronic Oral Toxicity Study in Albino Rats - CGA-15324 Technical," (G.A. Burdock and S. Fieser, Hazleton Laboratories of America, 5/22/81). CGA 15324 technical (purity = 90.6%) was fed in diet to albino rats (60-70/sex/dose) at 0, 0.3, 10, or 100 ppm for 2 years. Chronic NOEL = 10 ppm (There was decreased HCT and RBC, primarily in males at 100 ppm.) ChE NOEL = 0.3 ppm (RBC and plasma cholinesterase was inhibited in both sexes at $\geq$ 10 ppm. Some brain cholinesterase inhibition was observed in females at 100 ppm by 105 weeks.). Oncogenic NOEL > 100 ppm (There was no profenofos related oncogenicity observed at any dose). The study was previously reviewed as unacceptable due to lack of an analysis of dosing material (J. Remsen, 7/12/85). Upon submission of the requested information, the study has been upgraded to acceptable. No adverse effect. M. Silva, 6/17/97.

CHRONIC TOXICITY, DOG

**** 013-015 978775, 978895, 978899-900** "CGA 15,324 Technical: 6-Month Toxicity Study With Beagle Dogs," (Gfeller, W., Ciba-Geigy Limited, Basle, Switzerland; Project #: 790804, 6/17/81). Profenofos (88.1 - 89.3% pure) was fed in diet to Beagle dogs (7/sex/dose) at 0, 0.2, 2, 100 and 500 ppm for 6 months. Dogs (1/sex/dose) were kept for a 1 month post-treatment recovery period. Chronic NOEL = 2 ppm (Erythrocytes and hemoglobin concentration in both sexes at 500 ppm and hematocrit in males at 500 ppm were decreased. The carboxyesterase was significantly decreased in males weeks 26 and 31 (recovery) at $\geq$ 100 ppm.) Cholinesterase NOEL = 2 ppm (The plasma and RBC ChE activities were significantly decreased at $\geq$ 100 ppm in both sexes.) Acceptable. Possible adverse effect (significant inhibition of ChE). M. Silva, 6/19/97.

048 This volume is an exact copy of 013 978895.

ONCOGENICITY, MOUSE

**045 01691: G.A. Burdock, Study Director, "Twenty-Four Month Carcinogenicity Study in Mice - CGA 15324 Technical" Hazleton Laboratories of America, Project No. 483-133 [7/23/81]. CGA-15324 Technical, purity 90.6%, was admixed with the feed at concentrations of 0, 1, 30, or 100 ppm and fed to 65 HaM/ICR Swiss mice/sex/group for 24 months. Cholinesterase inhibition; NOEL = 1 ppm. No evidence of oncogenicity. ACCEPTABLE with minor variances. (J. Remsen, 7/12/85).

REPRODUCTION, RAT

** 093 & 094 132900 & 132902 "A Two-Generation Reproduction Study in Rats with CGA-15324 Technical," (J.L. Minor and A.G. Richter, Ciba-Geigy Environmental Health Center (EHC), Laboratory Study Number F-00102, 1/27/94). CGA-15324 technical (purity = 88.4%) was fed in diet to Sprague-Dawley rats (30/sex/dose) at 0, 5, 100, or 400 ppm for two generations. **Parental NOEL = 100 ppm** (Absolute body weight was decreased during premating for P0 males at 400 ppm. Absolute body weight was decreased during gestation and lactation for P0 females at 400 ppm. Both sexes of P0 rats showed mean body weight gain and mean cumulative body weight changes were significantly decreased at 400 ppm. P1 body weights were decreased throughout most of the premating period at 400 ppm (both sexes), as well as during gestation and lactation for P1 females at 400 ppm. Both sexes of P1 rats showed decreased mean body weight gain at 400 ppm and males also showed decreased mean cumulative body weight changes at 400 ppm. Food consumption for both sexes during premating were decreased at 400 ppm. P1 males showed increased incidence in dehydration during weaning and mating at 400 ppm.) **Reproduction NOEL > 400 ppm Pup NOEL = 400 ppm** (Pup weights were significantly decreased in both sexes on post-natal day 21, however pups had begun to ingest treated diet at this time.) ACCEPTABLE. (Kishiyama & Silva,

008 978906: "Reevaluation of the Validity of Three-Generation Rat Study with CGA-15324 Technical (Curacon)", Ciba-Geigy, {2/28/81]. Not a Chronic Study - Commentary only. UNACCEPTABLE (insufficient information). (J Remsen, 7/12/85).

TERATOLOGY, RAT

020 978902: H. Fritz, "Reproductive Study - Technical CGA-15324 (Test for teratogenic embryotoxic effects), Ciba-Geigy, Switzerland, [5/29/74]. CGA 15324 was administered by gavage at concentrations of 0, 10, 30 or 60 mg/kg to 20-27 female rats/group during gestation days 6-15. Food consumption was decreased for mid and high dose females. No adverse effects reported. UNACCEPTABLE. Insufficient information for assessment. (J. Remsen, 7/11/85).

** 087, 165 115634, 159648 "A Teratology Study of CGA-15324 Technical in Albino Rats," (Kung, A.H.C., Study Monitor, Science Applications, Inc.; CGA/SAI 282009; 7/22/82). "Supplemental Data and Response to Agency Review," (Meyer, L.S., 1/12/98; Novartis Crop Protection, Inc., Greensboro, NC). CGA-15324 (88.0% pure) was administered via gavage at concentrations of 0 (0.2% CMC), 10, 30, 60, 90, or 120 mg/kg to twenty-five Sprague-Dawley female rats during gestation Days 6 through 15. Maternal NOEL = 90 mg/kg (Clinical signs were increased and body weights were decreased at 120 mg/kg/day. Food consumption was reduced (14%) and mortality (16%) was increased at 120 mg/kg). Developmental NOEL = 120 mg/kg (No evidence of teratogenicity at any dose). Previously reviewed as unacceptable (Silva, 5/20/97), upon submission of the requested data (analysis of dosing material), the study is upgraded to acceptable. No adverse effect. M. Silva, 3/30/98.

TERATOLOGY, RABBIT

007 978905: Fritz, Study Director, "Report on CGA 15324 Technical Sig II Reproductive Study in Rabbits (Teratology Study in Rabbits). Ciba-Geigy Limited Basle, Switzerland Project No. 785565, [3/7/79]. CGA 15324, purity 89.5%, administered via gavage at concentrations of 0, 5, 15 and 30 mg/kg to 20 Chinchilla SPF female rabbits/group during gestation days 6-15. UNACCEPTABLE, due to major variance and insufficient information. (J. Remsen 7/11/85).

** 087, 165 115635, 159648: "Teratology Study (Seg II) in Albino Rabbits with CGA-15324 Technical," (Kung, A., Sponsor Monitor, Science Applications, Inc.; CGA/SAI 283003, 6/1/83). "Supplemental Data and Response to Agency Review," (Meyer, L.S.; Novartis Crop Protection, Inc., Greensboro, NC, 1/12/98). CGA-15324 (90.8% pure) was administered via gavage at concentrations of 0 (control), 30, 60, 90, or 175 mg/kg to sixteen mated, New Zealand White female rabbits/group during gestation Days 6 through 18. **Maternal NOEL =** 30 mg/kg/day (Deaths at 175 mg/kg/day, clinical signs at $\geq$ 60 mg/kg/day were increased and macroscopic pathology was increased at 175 mg/kg/day.) **Developmental NOEL =** 175 mg/kg. Previously reviewed as unacceptable (Silva, 5/27/97). Upon submission and review of the requested information (analysis of dosing material), the study is upgraded to acceptable. (Silva, 3/30/98).

GENE MUTATION

** 086 115630 "CGA-15324 Technical *Salmonella* and *Escherichia*/Liver-Microsome Test - Gene Mutation Test," (B. Ogorek, Ciba-Geigy Limited, Laboratory Study Number 901526, [2/1/91]. Basle, Switzerland). CGA 15324 (purity = 90%) was used on *Salmonella typhimurium* TA 98, TA100, TA1535 and TA1537 and *Escherichia coli* WP2 uvrA bacterial strains in a gene mutation assay at concentrations of 312.5, 625, 1250, 2500 and 5000 µg/plate (48 hour exposure; +/- S9). CGA 15324 did not induce gene mutation under the conditions of this test. Positive controls functioned as expected. ACCEPTABLE. (Kishiyama & Silva, 5/12/97).

058 045634 "CGA-15324: *Salmonella*/Mammalian-Microsome Mutagenicity Test", (Arni, P. and D. Müller, Experiment No. 78/2531, Ciba-Geigy Limited, Basle, Switzerland, 4/27/78). CGA 15324 (purity not stated) was used in a mutagenicity assay with *Salmonella typhimurium* strains TA 98, TA100, TA1535 and TA1537 at concentrations of 0, 5, 15, 45, 135 and 405 µg/0.1 ml (48 hours exposure). There was no evidence of mutagenicity at any dose with CGA 15324 treatments, compared to negative controls. UNACCEPTABLE, but possibly upgradeable (insufficient information). (Kishiyama & Silva, 6/11/97).

056 045631, "CGA-15324: L5178Y/Tk + / - Mouse Lymphoma Mutagenicity Test," (F.F. Strasser, Ciba-Geigy Limited, Basle, Switzerland, Experiment Number 811491, 2 /17/82). CGA 15324, purity not stated, was used at concentrations of 0, 0.078, 0.156, 0.313 and 0.625 µl/ml on mouse lymphoma cells (+/- S9) in a mutagenicity assay. There were no mutagenic effects reported in this study. UNACCEPTABLE, not upgradeable. The study was not performed according to FIFRA Guidelines. (Kishiyama & Silva, 6/10/97).

CHROMOSOME EFFECTS

020 978910: H. Fritz, "Dominant Lethal Assay on CGA 15324 Techn. - Mouse (test for cytotoxic or mutagenic effects on male germinal cells), Ciba-Geigy, [12/10/74]. CGA 15324, purity not stated, administered by a single gavage at concentrations of 0, 35 and 100 mg/kg to 12 NMRI male mice/group. UNACCEPTABLE, due to major variances and insufficient information. (J. Remsen 7/11/85).

058 045635. Duplicate of 978910.

** 086 115631 "CGA-15324 Technical: Micronucleus Test, Mouse," (T. Hertner, Ciba-Geigy Limited, Basle, Switzerland, Laboratory Study Number 891212, [2/19/90]). CGA 15324 (purity = 90.7%) was gavaged in a single treatment to Tif: MAGF, SPF, NMRI-derived mice. Initially (Part 1) mice were exposed to 200 mg/kg, then were sacrificed at 16, 24, and 48 hours (8 animals/sex/time point) and their bone marrow was examined for micronucleated polychromatic erythrocytes (MPE). Subsequently (Part 2) mice were treated at 0, 50, 100 or 200 mg/kg, then sacrificed at 48 hours for evaluation of MPE. NOEL = 50 mg/kg. There were no treatment-induced effects at any dose. The positive controls performed as expected. ACCEPTABLE. (Kishiyama & Silva, 5/15/97).

**086 115633:"CGA-15324 Technical: Chromosome Studies on Chinese Hamster Ovary Cell Line CCL61 *In Vitro*," (F.F. Strasser, Ciba-Geigy Limited, Basle, Switzerland, Laboratory Study Number 891251, 1/30/90.) CGA 15324 (purity = 90.7%) was used on Chinese Hamster ovary cells (CCL61) in 3 experiments. Part 1 used doses of 0, 9.38, 18.75, 37.5 and 75 ug/ml. Part 2 and 3 used doses of 0, 4.69, 9.38, 18.75 and 37.5 ug/ml to test for induction of chromosome aberrations. Exposure times were 3 hours for Part 1 & 2 and 24 hours for Part 3 (2 cultures/dose). Parts 1 & 3 were with S9 and Part 2 was without S9. Chromosomal aberrations did not significantly increase under study conditions with CGA 15 324 treatments. ACCEPTABLE. Absence of multiple harvest times. (Kishiyama & Silva, 5/20/97).

058 045632 "CGA-15324: Nucleus Anomaly Test in Somatic Interphase Nuclei, Chinese Hamster," (Hool, G., Ciba-Geigy Limited, Basle, Switzerland, Experiment No. 791557,1/28/81). CGA 15324 (purity not stated), was administered by gavage on 2 consecutive days, at concentrations of 0 (0.7% CMC), 13, 26 and 52 mg/kg to Chinese hamsters (6/sex/dose). At 24 hours after the second treatment, the animals were sacrificed and bone marrow was removed. Smears were made from bone marrow cells and the cells were analyzed for potential aberrations. There was no evidence of chromosomal aberration in this study. UNACCEPTABLE, not upgradeable (major deficiencies and insufficient information). (Kishiyama & Silva, 6/11/97).

DNA DAMAGE

** 058 & 086 045633 &115632, "CGA-15324: Autoradiographic DNA Repair Test on Rat Hepatocytes," (Puri, E., Ciba-Geigy Ltd., Basle, Switzerland, Exp. #: 811490; 2/16/82). "CGA-15324 Technical: Autoradiographic DNA Repair Test on Rat Hepatocytes," (D. Geleick; Agricultural Division, Ciba-Geigy Limited, Basle, Switzerland, Laboratory Study Number 811490, [4/10/91]). In experiment 045633 CGA 15324 (purity = 91.8%) was used at 0 (medium + DMSO), 0.016, 0.088, 0.4 and 2 nl/ml and in experiment 115632 was used at 0, 0.02, 0.12, 0.58 and 2.91 µg/ml on rat hepatocytes for evaluation of DNA damage. Results indicated no induction of DNA damage by CGA 15324. ACCEPTABLE. (Kishiyama & Silva, 5/15/97).

NEUROTOXICITY

** 022 978886: B.M. Phillips, Study Director, "Neurotoxicity Study with CGA 15324 38% E.C. in Chickens", IBT No.8580-10426, Industrial Bio-Test Laboratories, [6/6/77]. CGA 15324, 38% E.C.(10% Toximull H, 39% Tenneco 500), was administered *via* gavage at concentrations of 0 (corn oil), 29.2, 58.5, 117.0, or 234 mg/kg body weight to 1-year old female chickens (10 in the control, 15 in each of the two lower doses and 40 for the 117 mg/kg group). Cholinesterase inhibition was seen in the first several days post-treatment. All (30) hens in the 234.0 mg/kg group died within 4 days. No treatment related neural changes reported. ACCEPTABLE with minor variances. (J. Remsen, 7/12/85). NOTE: This study is not on the IBT tracking list of the USEPA and may be invalid. (Gee, 6/26/97).

024 978841: "Acute Oral LD_{50} and Neurotoxicity Study of Technical CGA 15324 in Domestic Fowl (*Gallus domesticus*), CIBA Geigy, Project No.: Siss 2850, [1/3/74]. CGA 15324 Technical, purity not stated, was administered via gavage at concentrations of 21.7, 46.4, or 60 mg/kg to 2 white leghorn chickens/sex/group. Only low dose group survived for pathological evaluation. TOCP control gave positive signs of neurotoxicity. No neurotoxic damage observed in the low dose group. UNACCEPTABLE, insufficient information. (J. Remsen, 7/12/85).

020 978885: M.K. Johnson, "Organophosphorus Esters Causing Delayed Neurotoxic Effects", U.K. Medical Research Council Toxicology Research Unit, [7/17/75]. No useful information. (J. Remsen, 7/11/85).